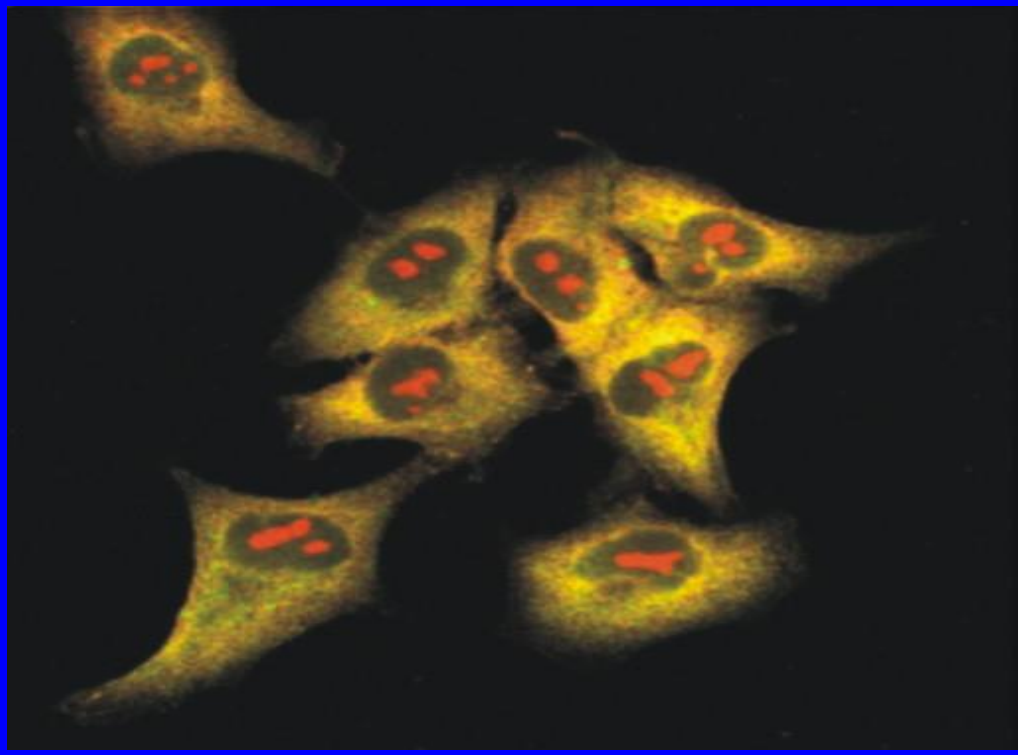
Introduction to the mTOR Pathway and Protein Translation

ESMO, Sitges, February 28th, 2014



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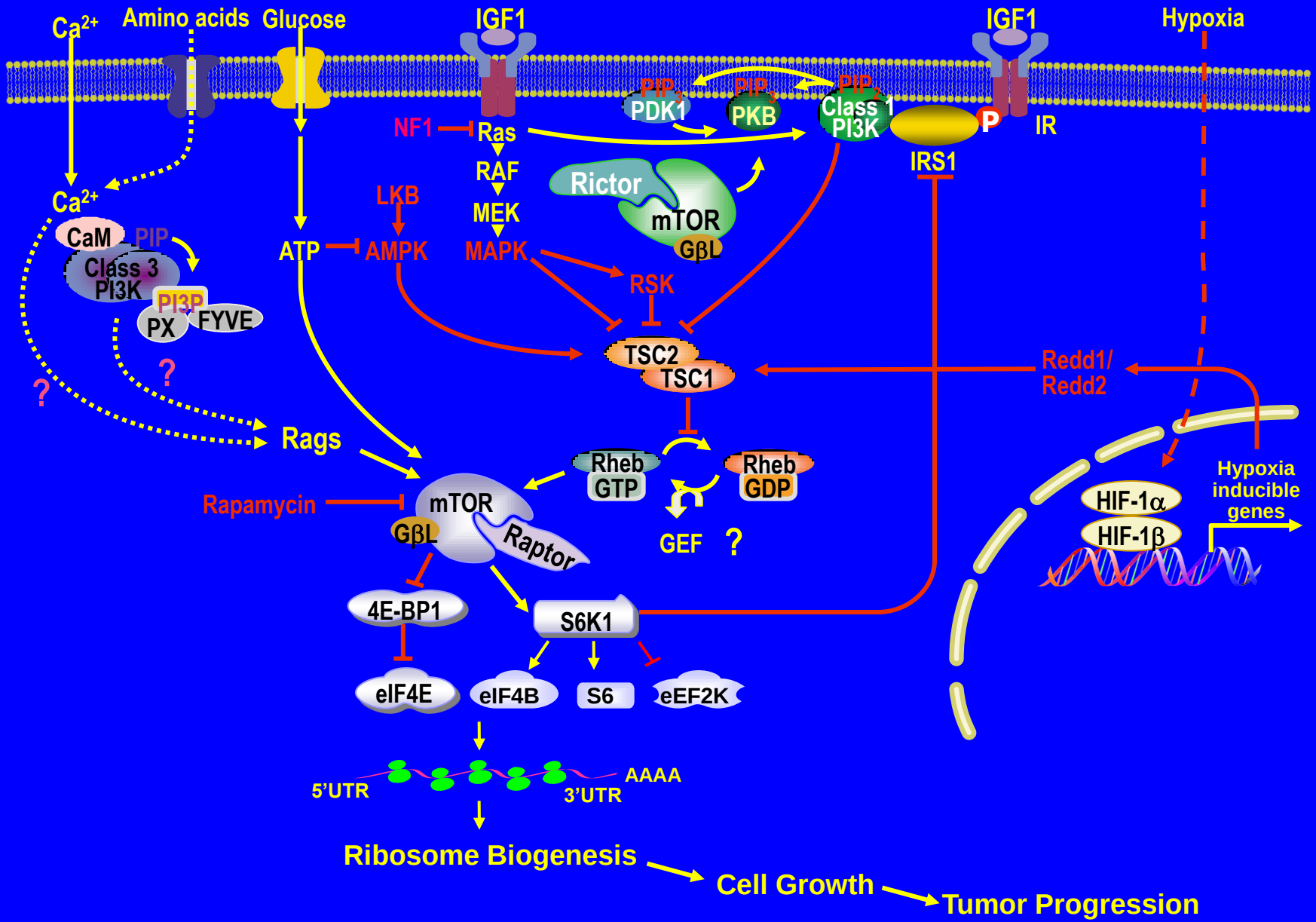
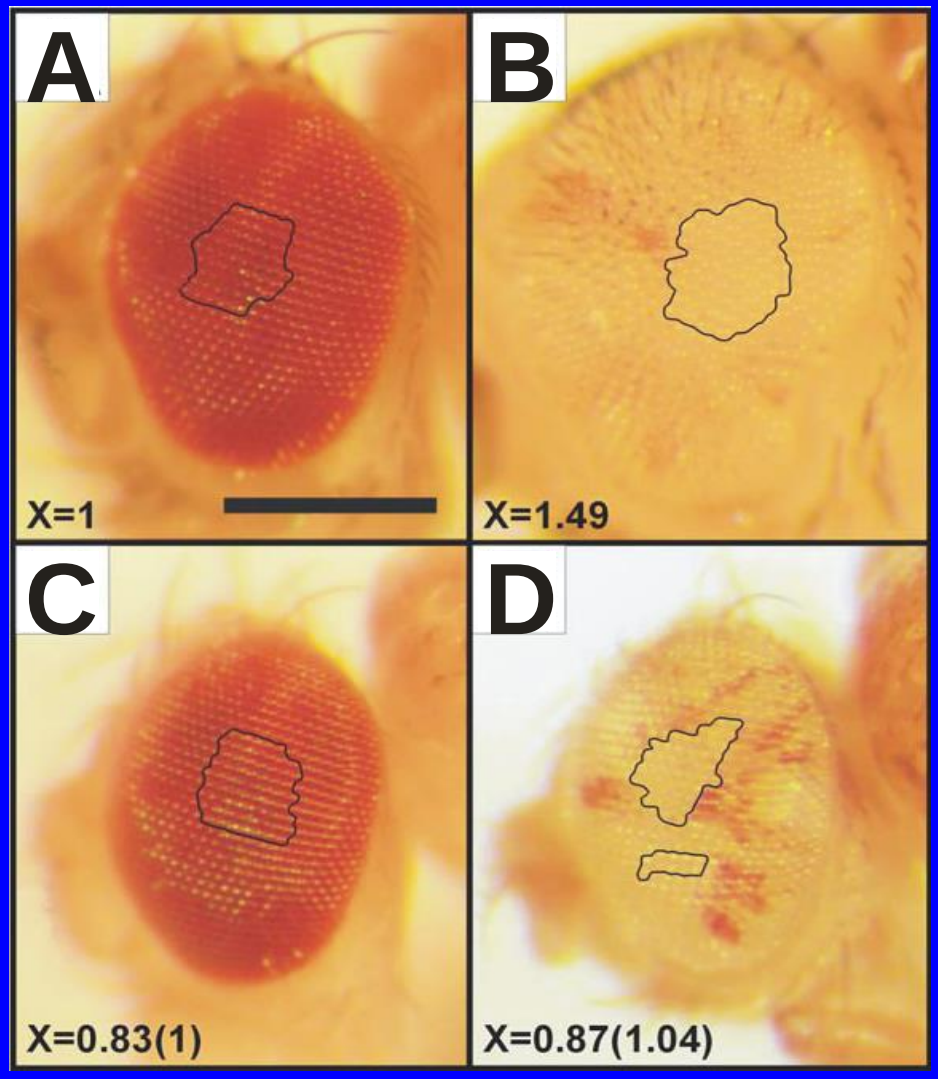
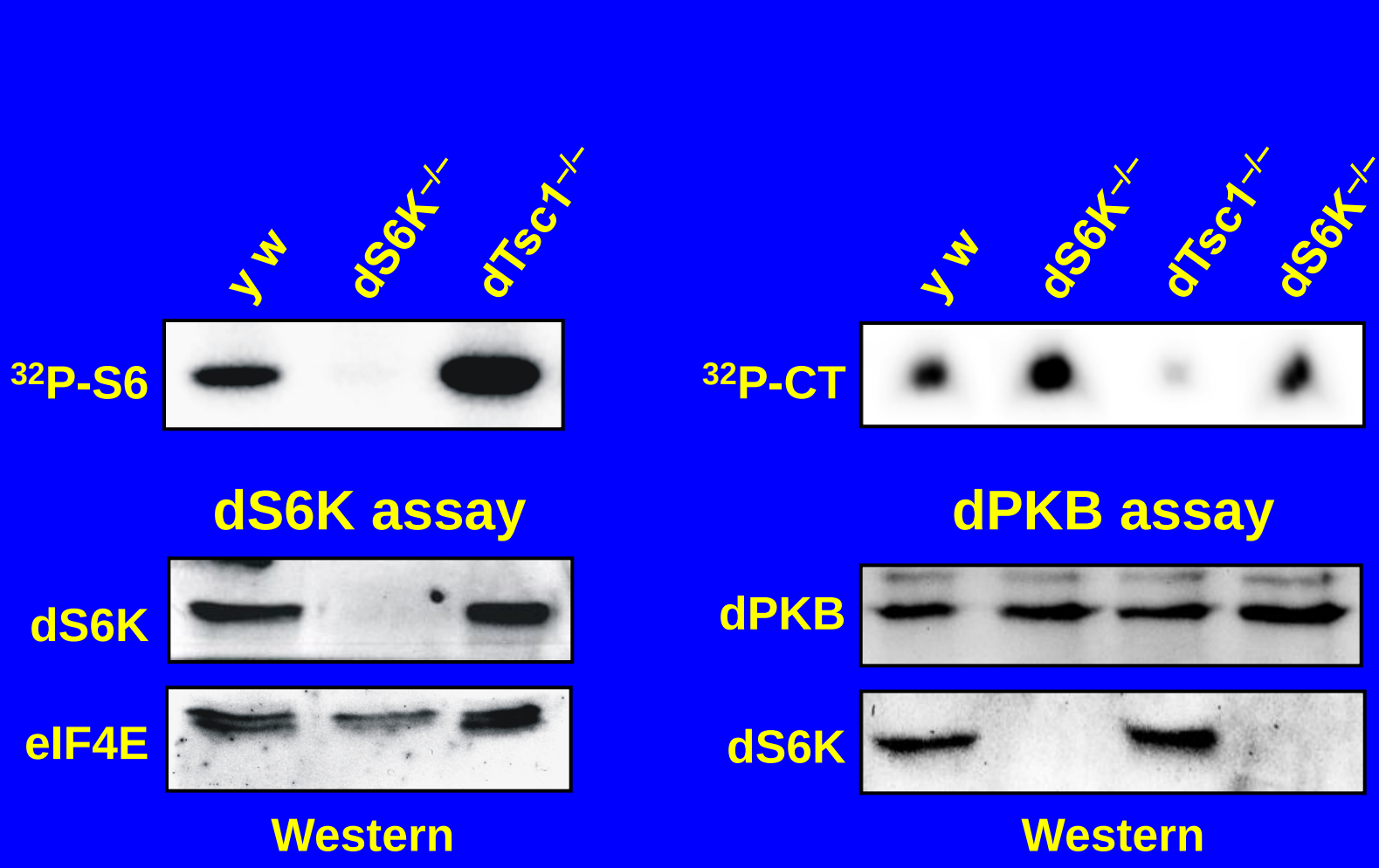
mTOR/S6K1 Signaling



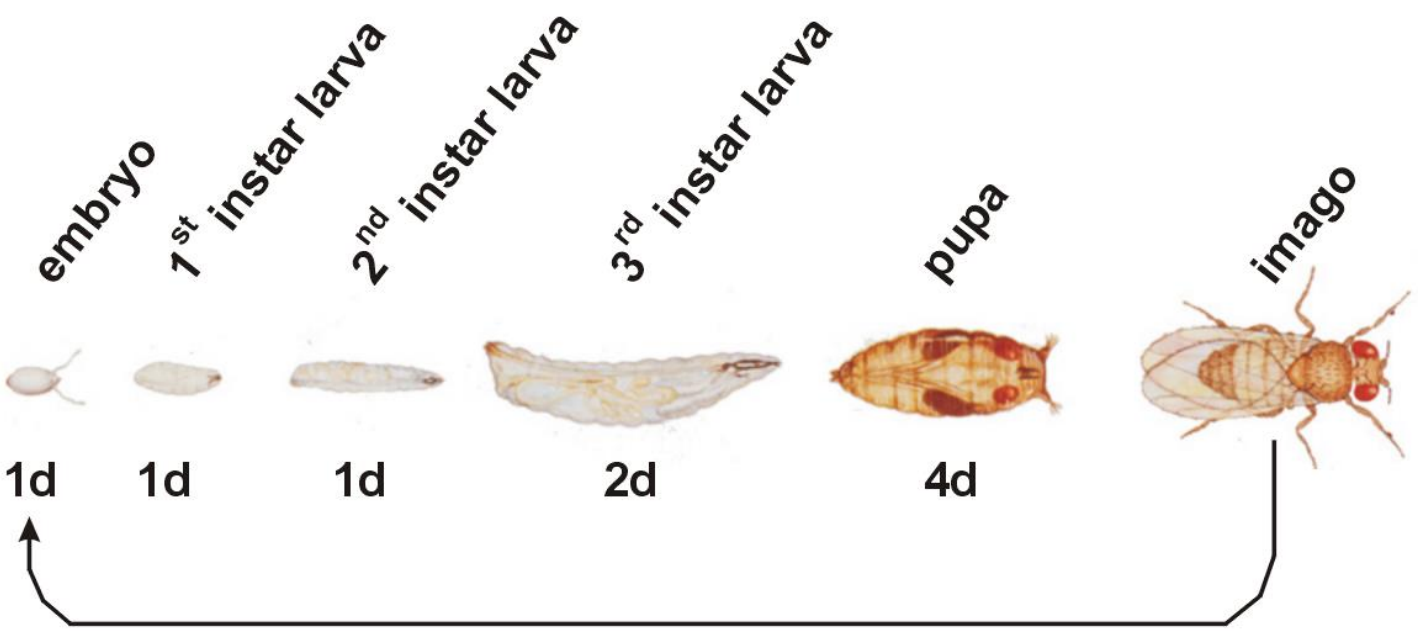
dS6K $^{-/-}$ suppresses dTsc1$^{-/-}$



dTsc negatively regulates dPKB via dS6k

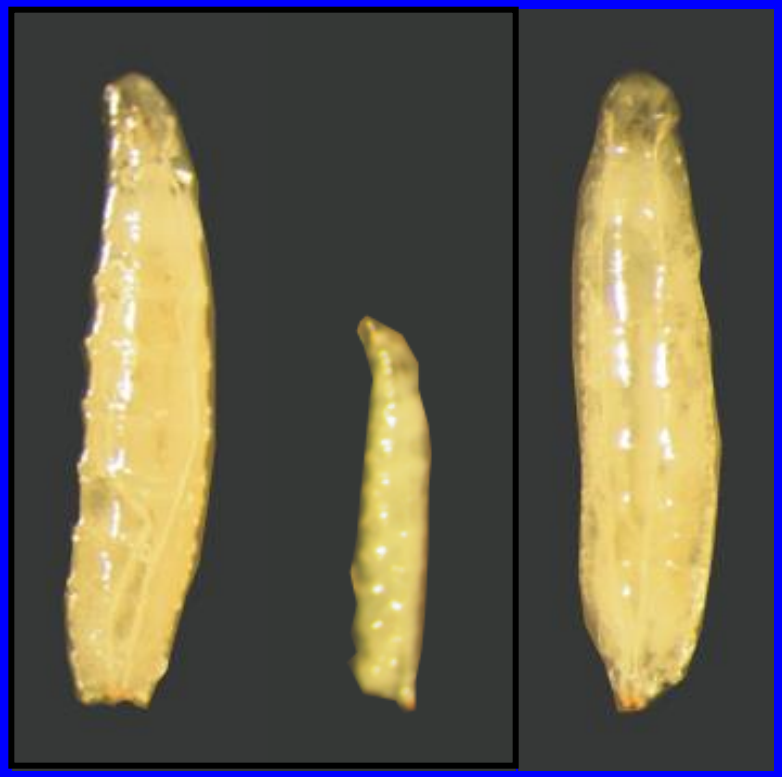


The *Drosophila* life cycle



Modified from: http://quantgen.med.yale.edu

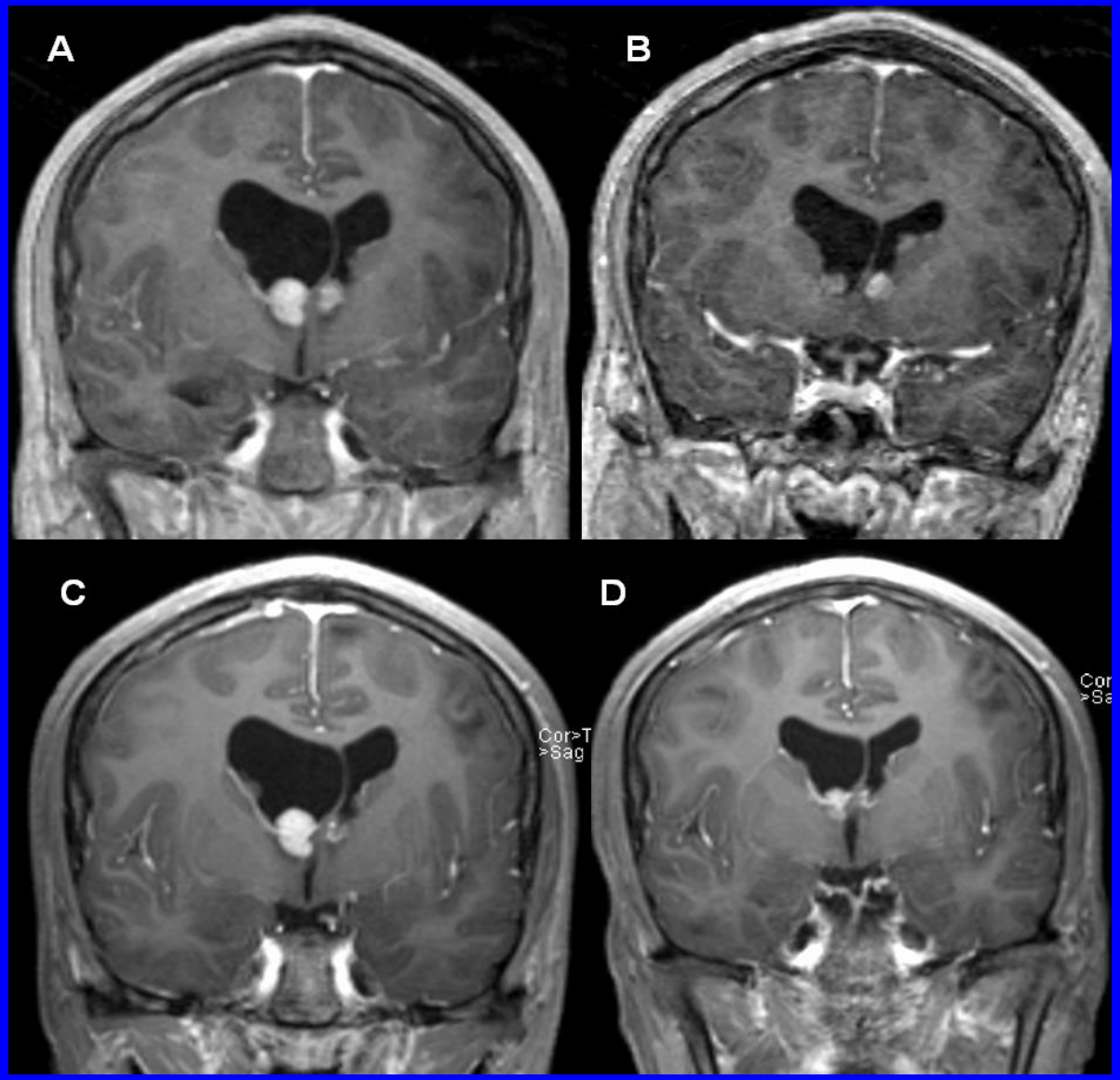
dTSC1$^{-/-}$ larvae



***dTsc1*:**	**+/+**	**–/–**	**–/–**
RAD001:	**–**	**–**	**+**

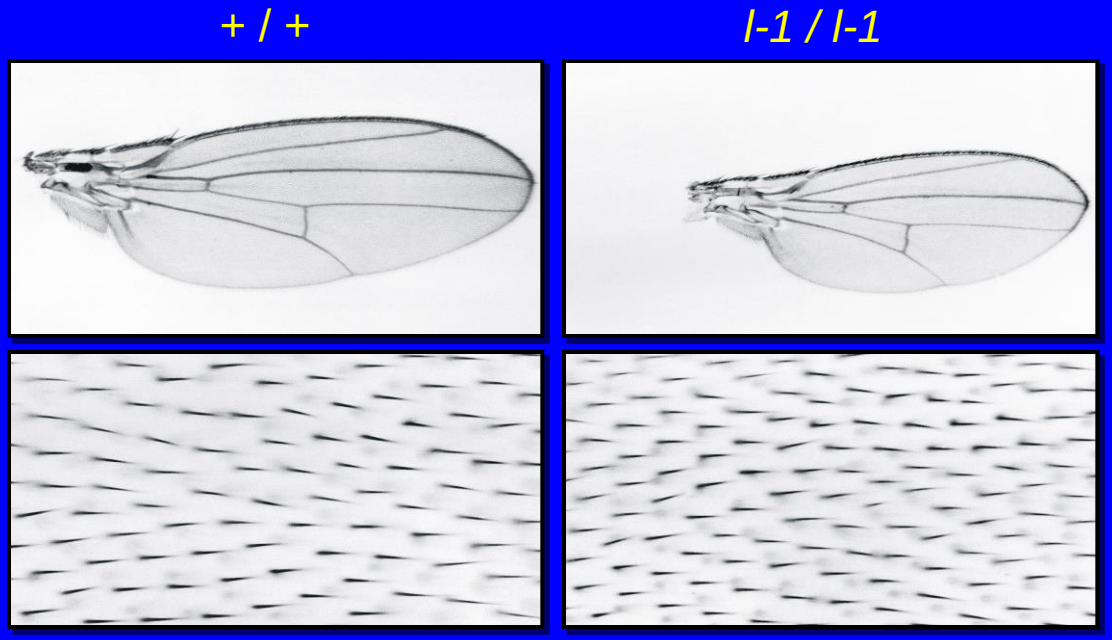
dTSC1$^{-/-}$ flies

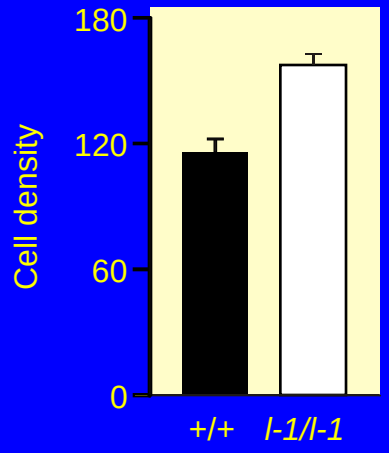
Effect of Treatment on SEGAs

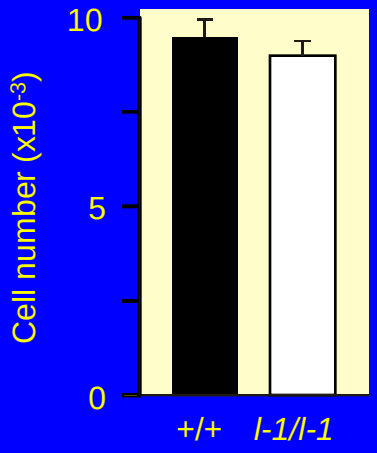


Effect of dS6K loss of function on cell growth

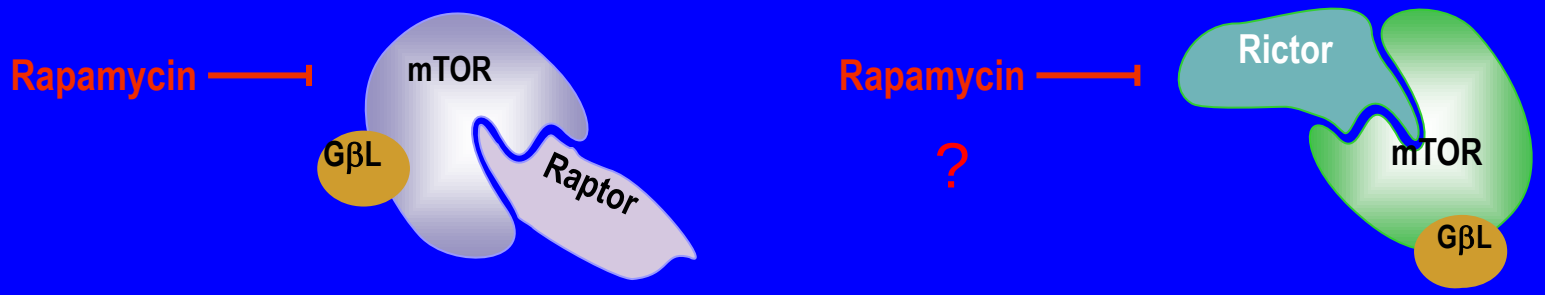
Cell Size Defect in Wings



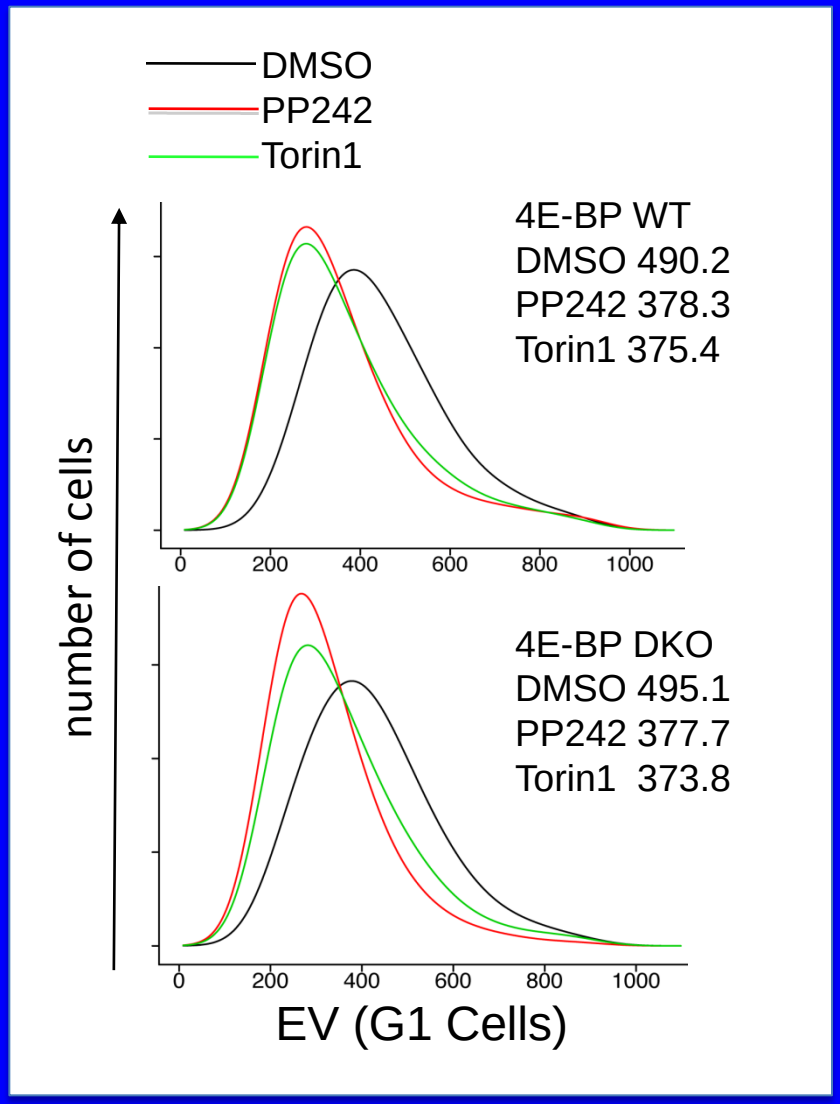




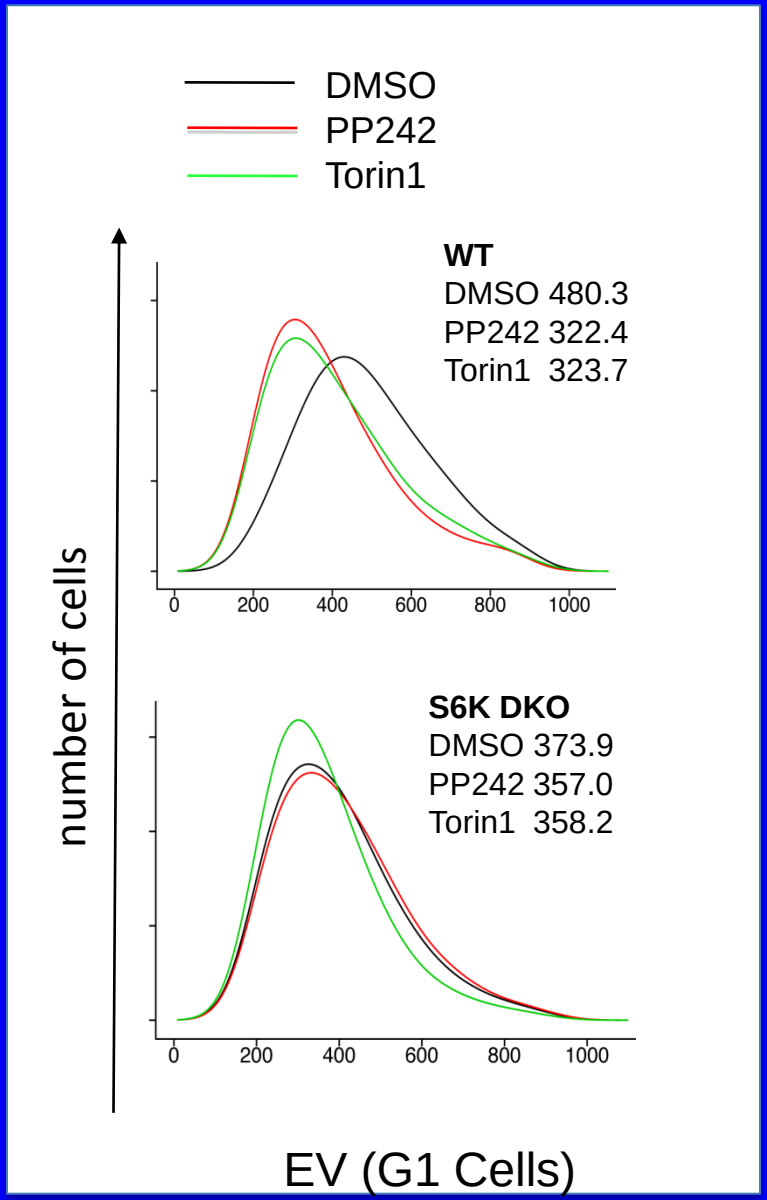
mTORC1 versus mTORC2: Role of PP242 & Torin



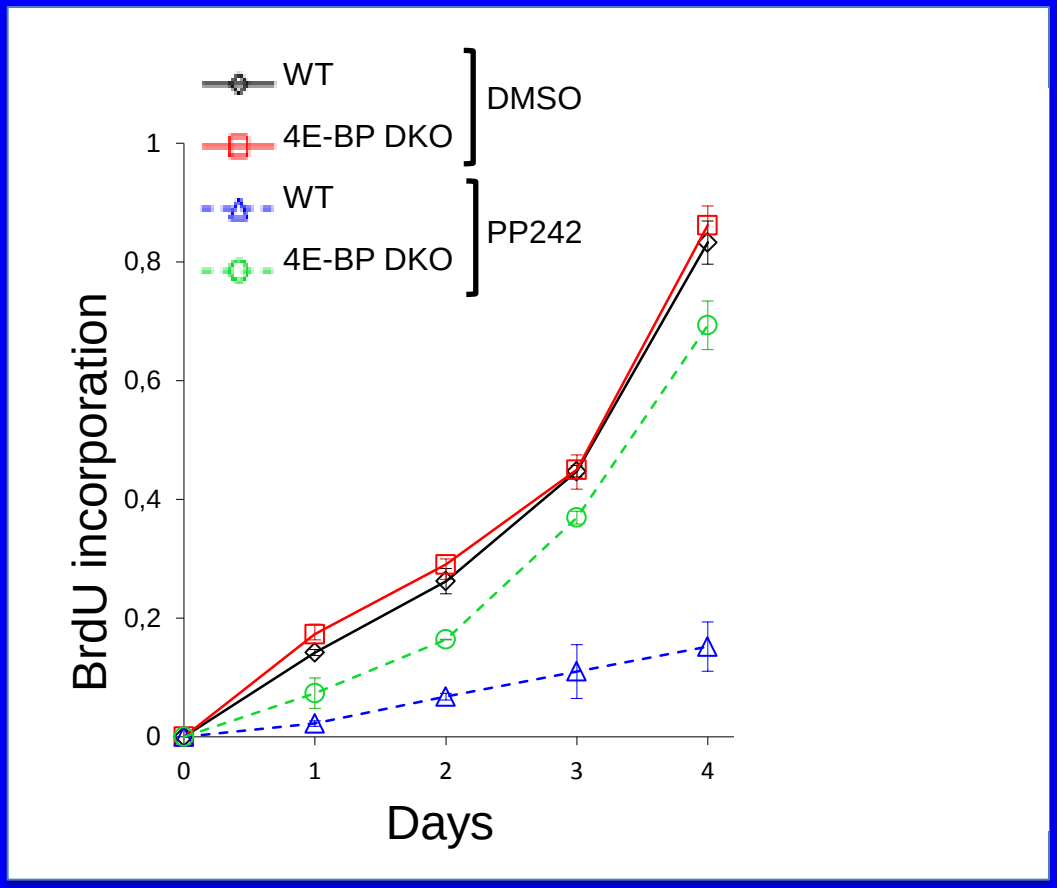
Effect of 4E-BPs on Cell Size



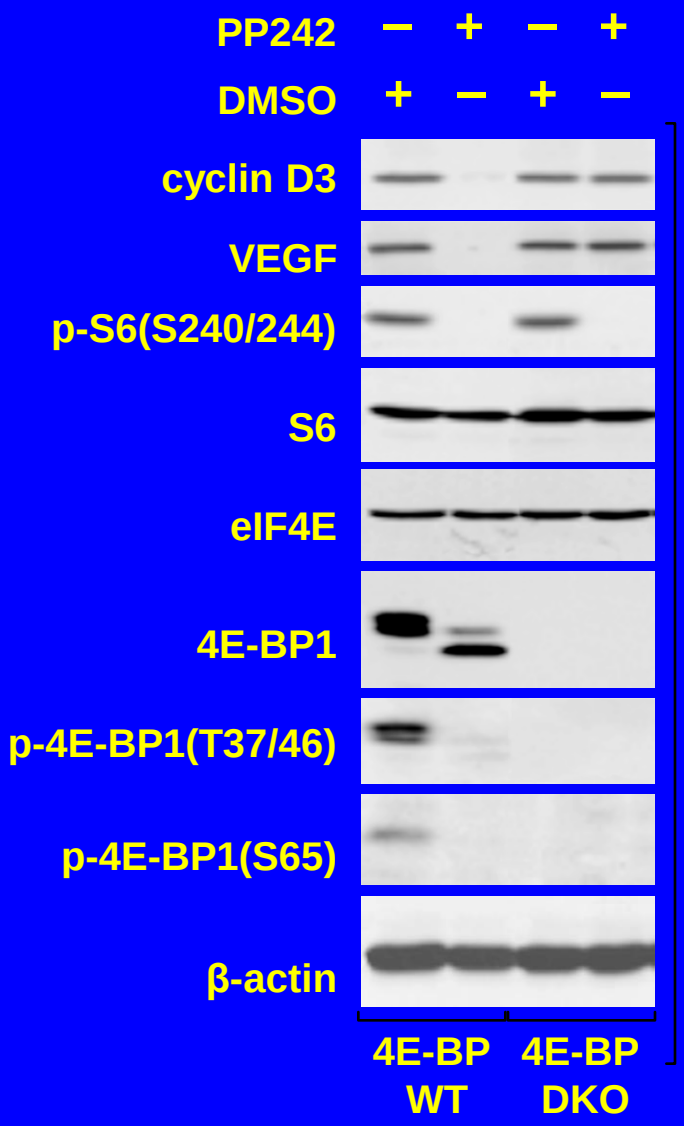
Effect of S6Ks on Cell Size



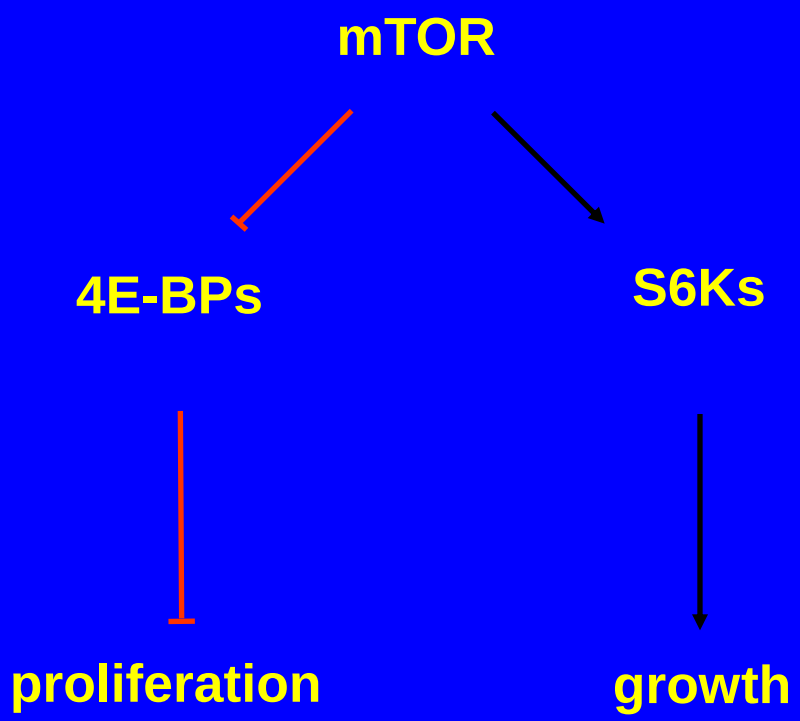
Effect of PP242 on Cell Proliferation



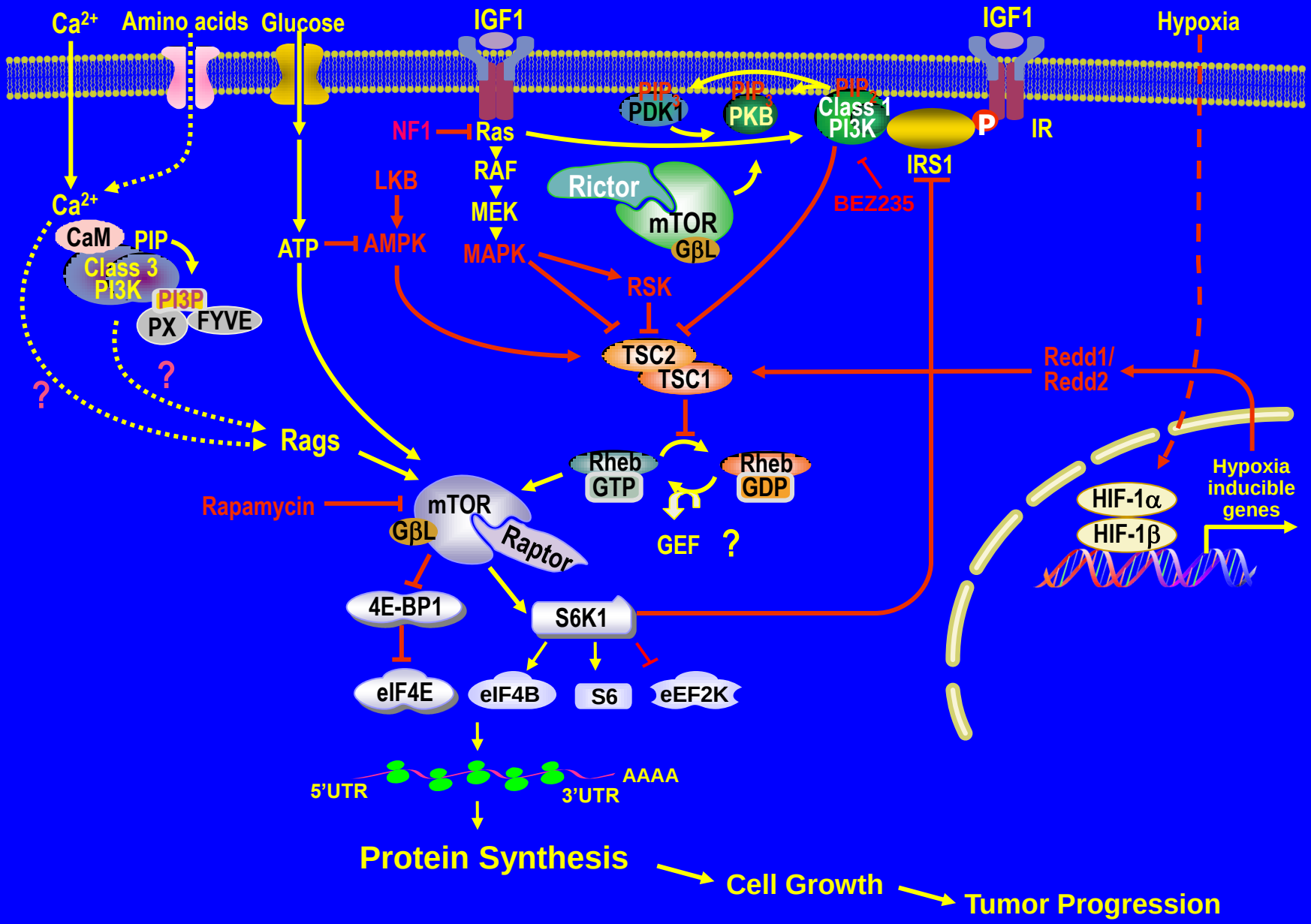
Effect of PP242 on Cell Cycle Regulators



“Division of labor” downstream of mTOR



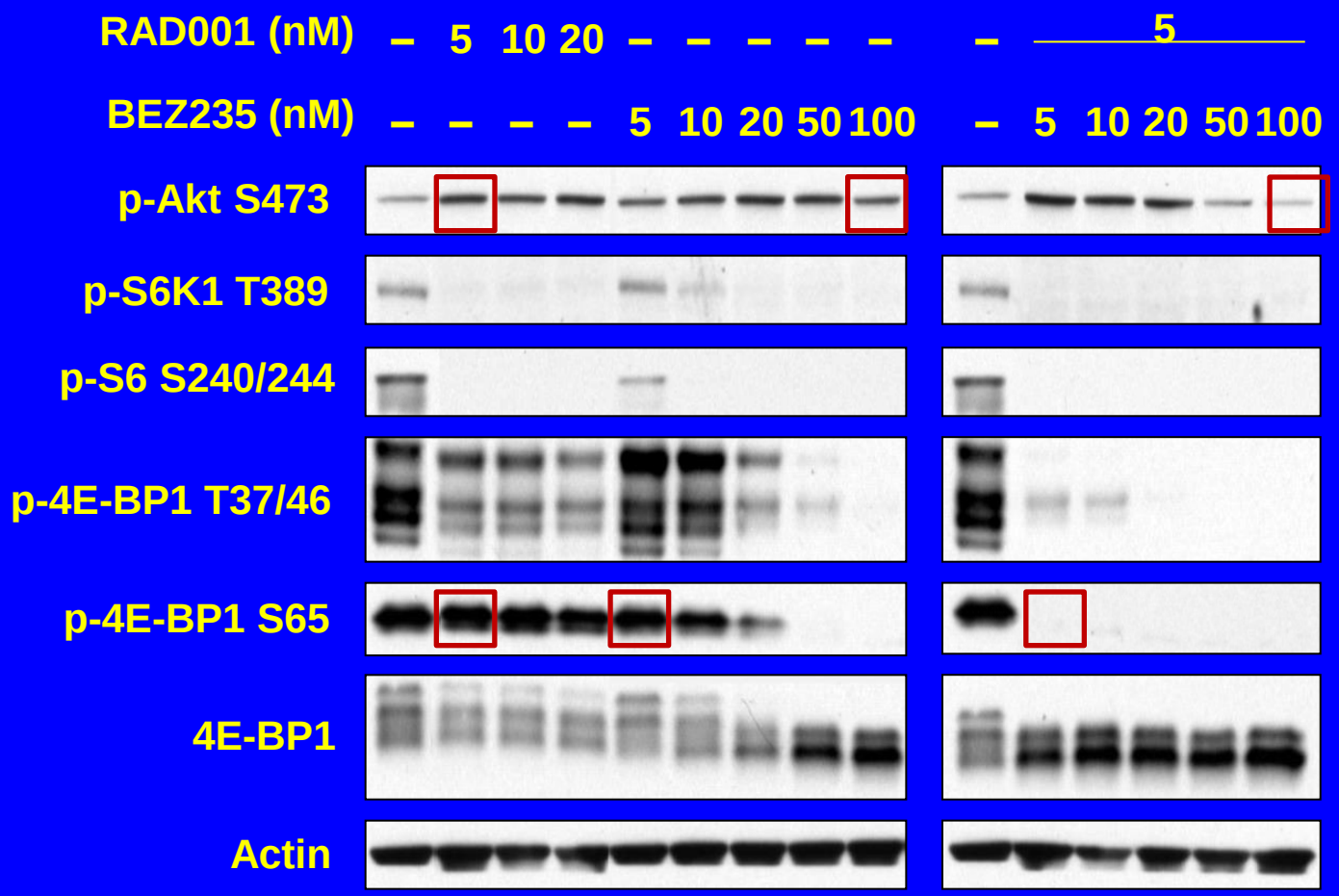
mTOR signaling pathway



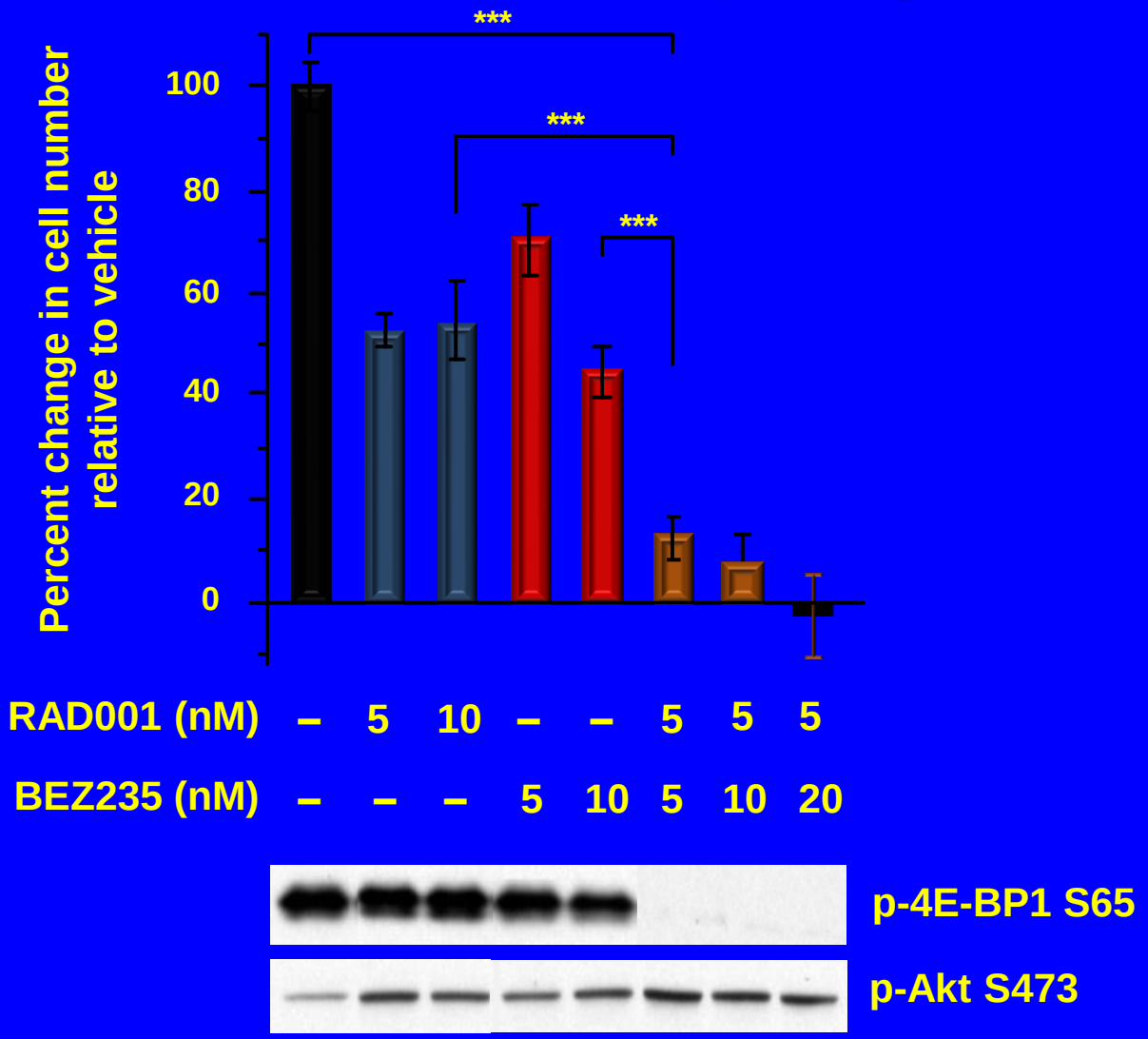
Human Hepatocellular Carcinoma (HCC)

- Is the 5th most common cancer in the world
- is the 3rd cause of cancer related mortality
- 80% of HCC have hyperactive mTORC1 signaling
- Any agent leading to chronic liver damage is a risk factor for HCC, such as:
  - Infection with either Hepatitis B or C viruses
  - Exposure to aflatoxins
  - Alcoholism
  - Non-alcoholic hepatosteatosis (NASH), metabolic disorders-mainly obesity

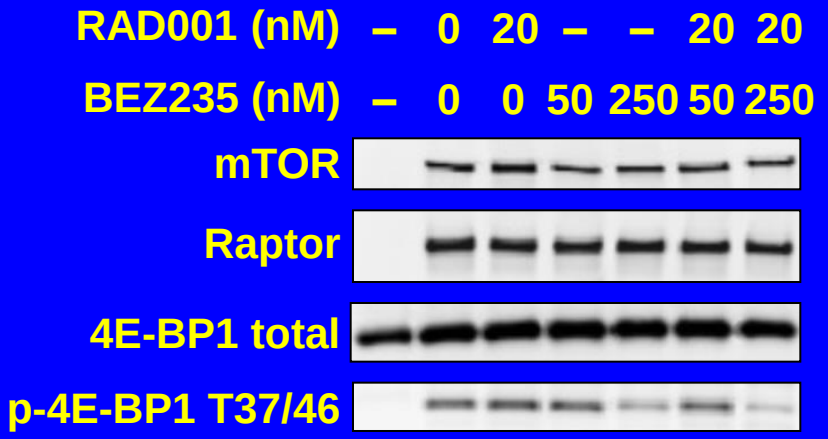
RAD001 and BEZ235 synergistically inhibit mTOR signaling

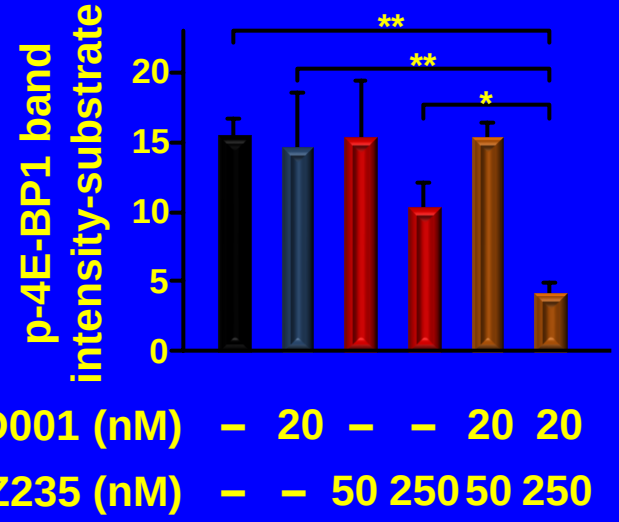


RAD001/BEZ235 Inhibition of Proliferation Parallels 4E-BP1 Phosphorylation



RAD001 and BEZ235 Synergistically Inhibit of mTORC1 Kinase *in vitro*





DEN HCC Mouse Model ~ Human HCC with Bad Prognosis

2 weeks

46 weeks

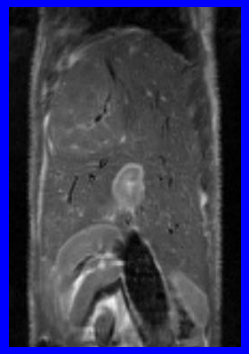
50 weeks

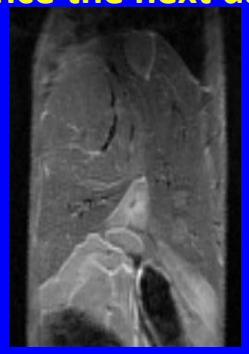
Treatment

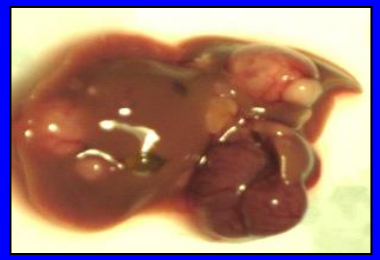
Inject with DEN (50mg/Kg BW)

MRI
Start treatment

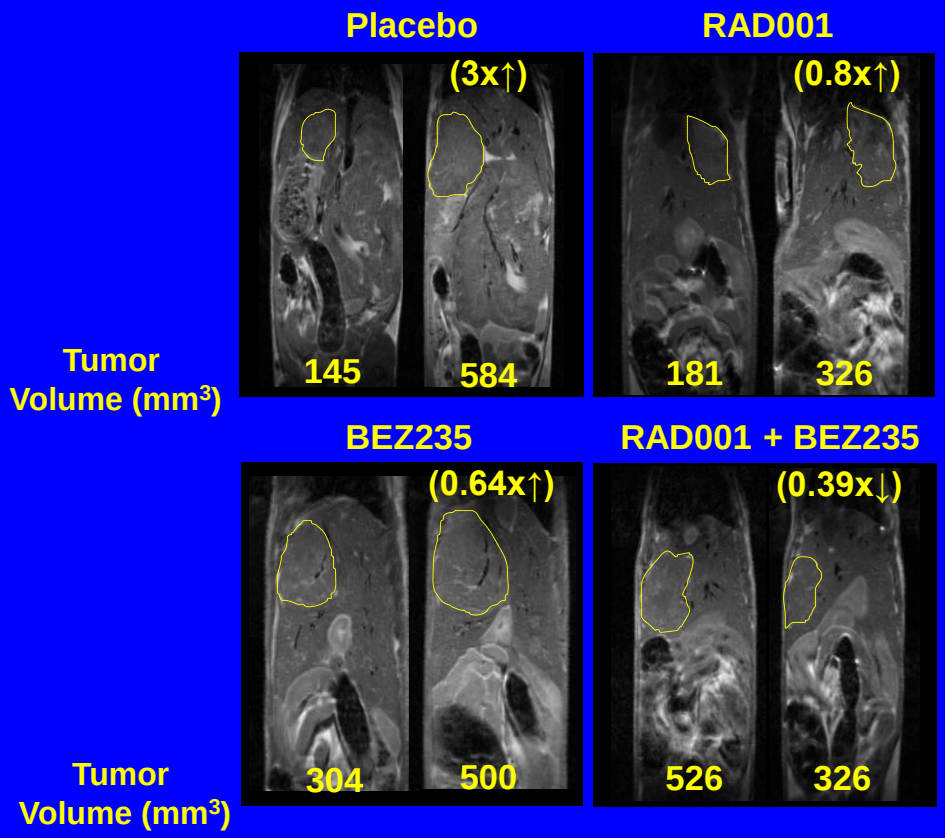
MRI
Sacrifice the next day

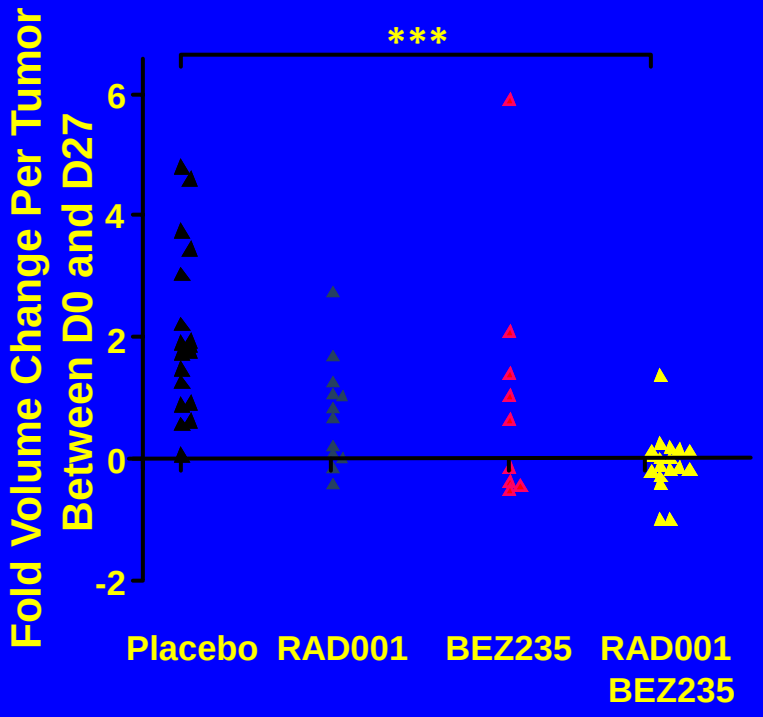




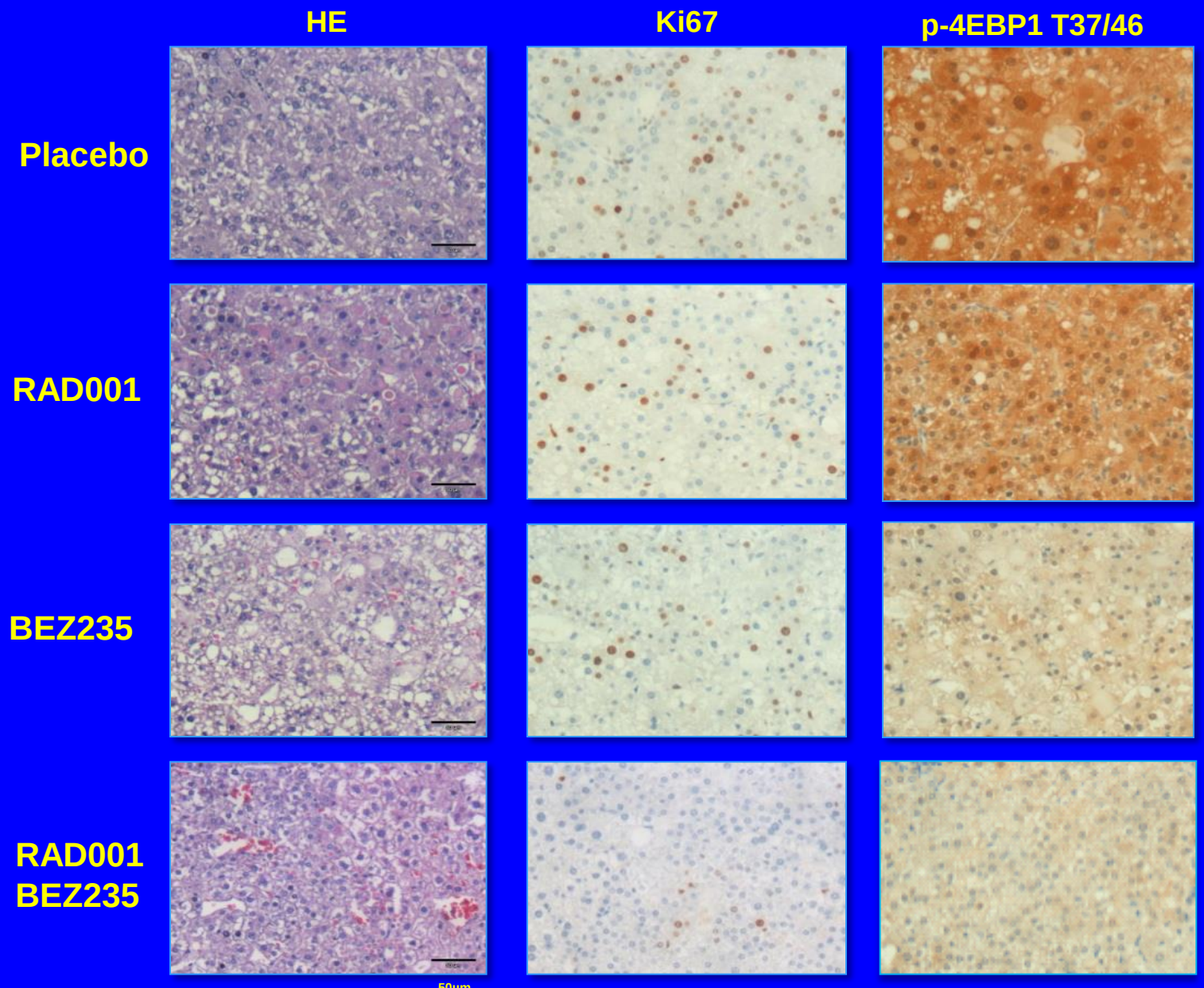


The RAD001/BEZ235 Inhibits HCC Better than Single Agents Alone

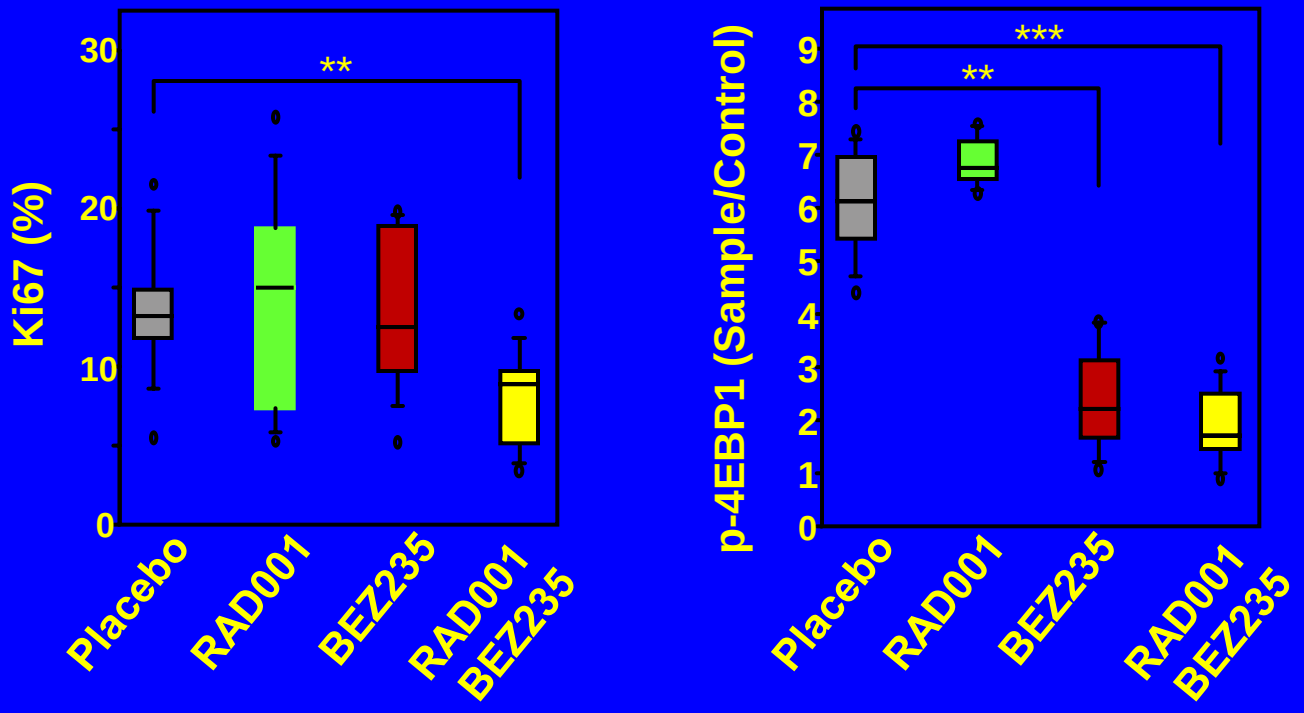




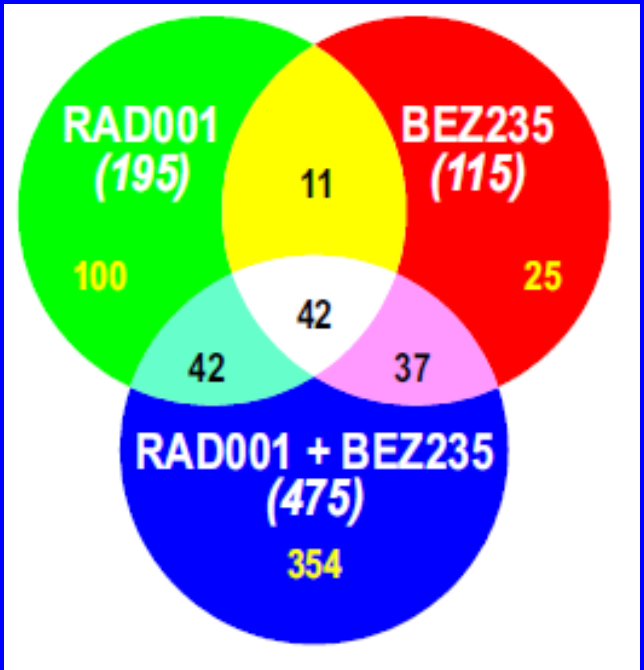
RAD001/BEZ235 Inhibit HCC Better than Single Agents Alone

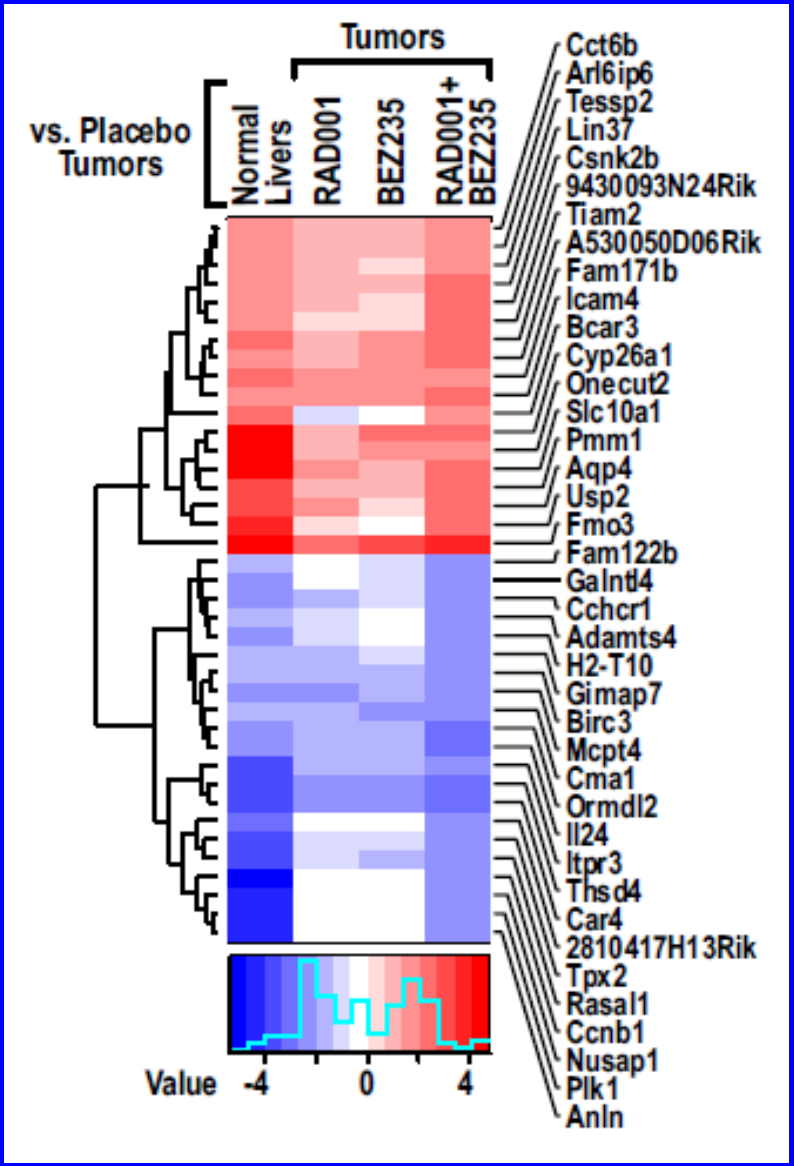


No statistical significance for p-4EBP1 between BEZ235 alone and combination



RAD001/BEZ235 Causes the Largest Number of Genes to Revert to Normal



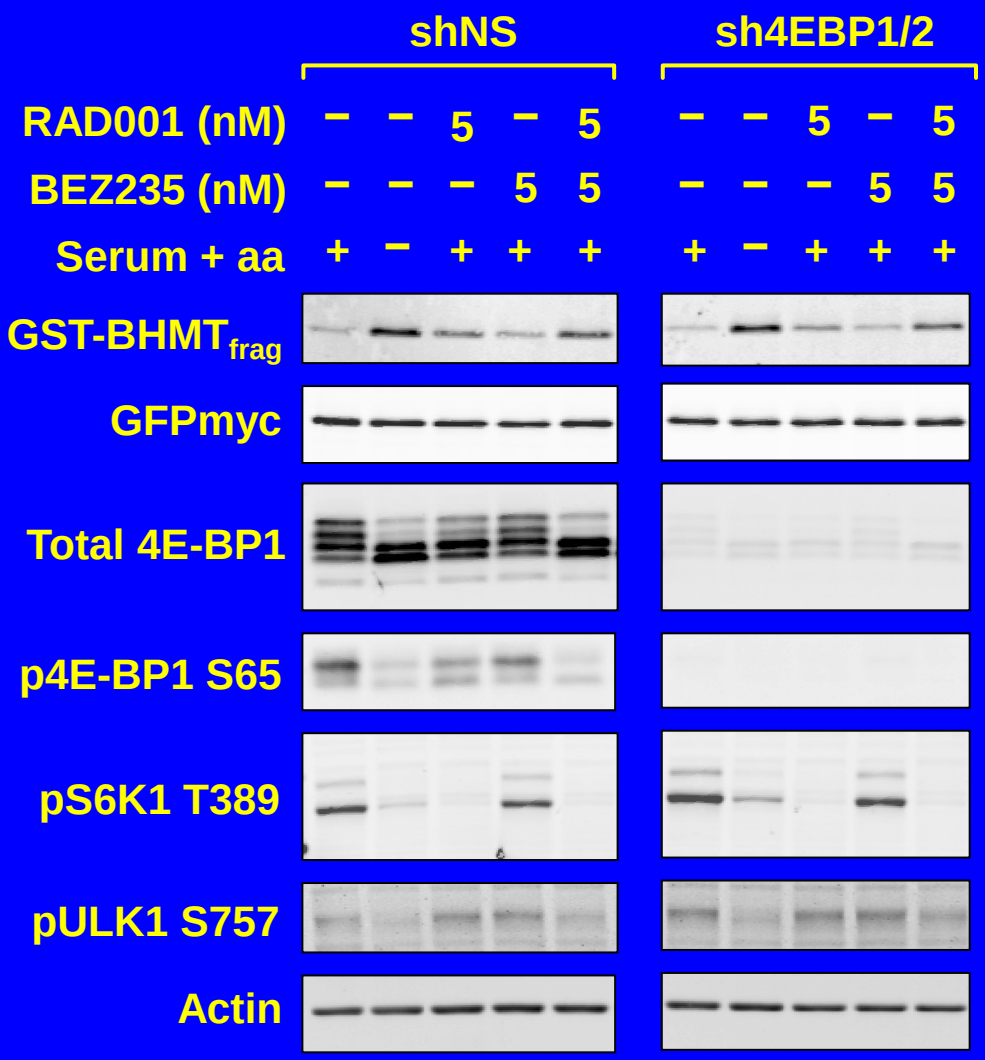


Pair-wise Comparison of Autophagy Genes between Placebo Tumors and Normal Livers

	[Placebo tumors] vs [Placebo livers]		
Gene ID	**logFC**	**p value**	**FDR**
Atg2b	**-0.262**	**0.064**	**0.218**
Atg3	**-1.212**	**0.000**	**0.000**
Atg5	**-0.600**	**0.000**	**0.000**
Atg7	**-1.201**	**0.000**	**0.000**
Atg9b	1.727	0.051	0.185
Atg10	**-0.430**	**0.015**	**0.075**
Atg16l1	**-0.326**	**0.005**	**0.033**
Becl1	-0.057	0.676	0.861
Ulk1	0.764	0.008	0.047
Ulk2	**-0.936**	**0.000**	**0.000**
Map1lc3a	**-1.380**	**0.000**	**0.000**

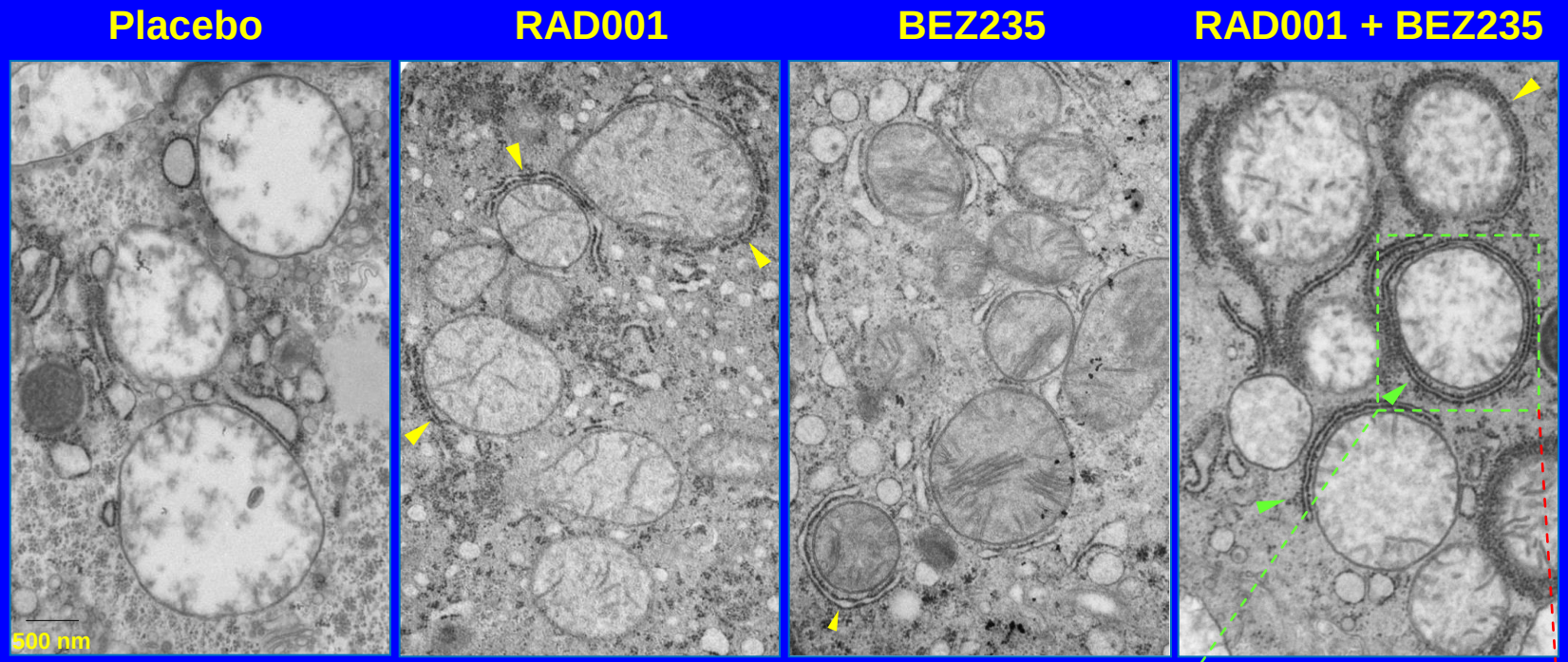
Does autophagy play a role in suppressing HCC following the treatment with the combination of RAD001 and BEZ235?

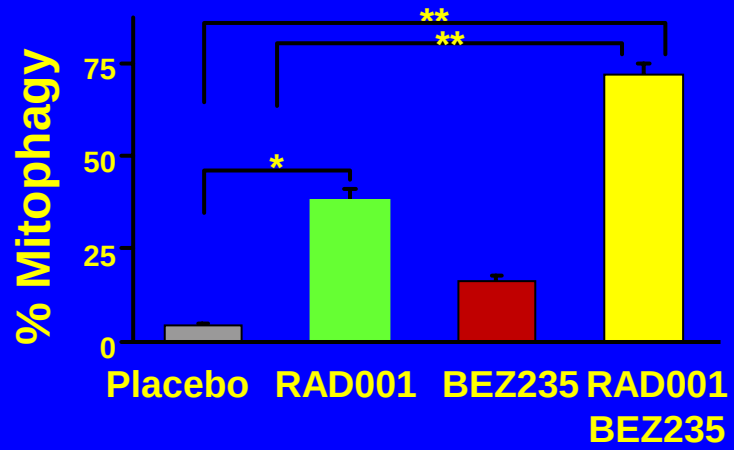
RAD001 and BEZ235 versus Autophagic Response

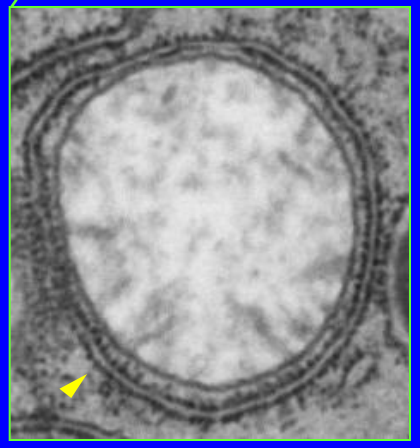


Does autophagy play a role in suppressing HCC following treatment with the drug combination in vivo?

RAD001/BEZ235 Effect Autophagosomes

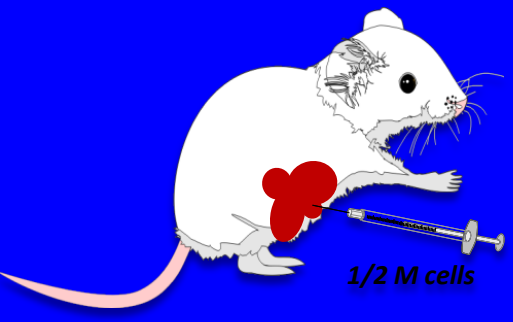


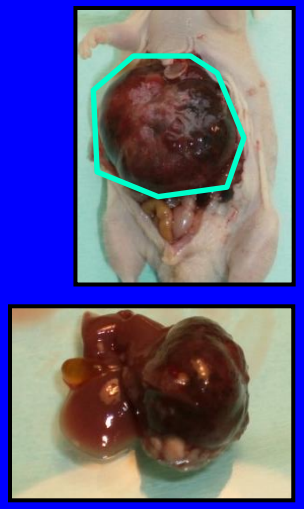




Orthotopic HCC model : human HCC cell lines in nude mice

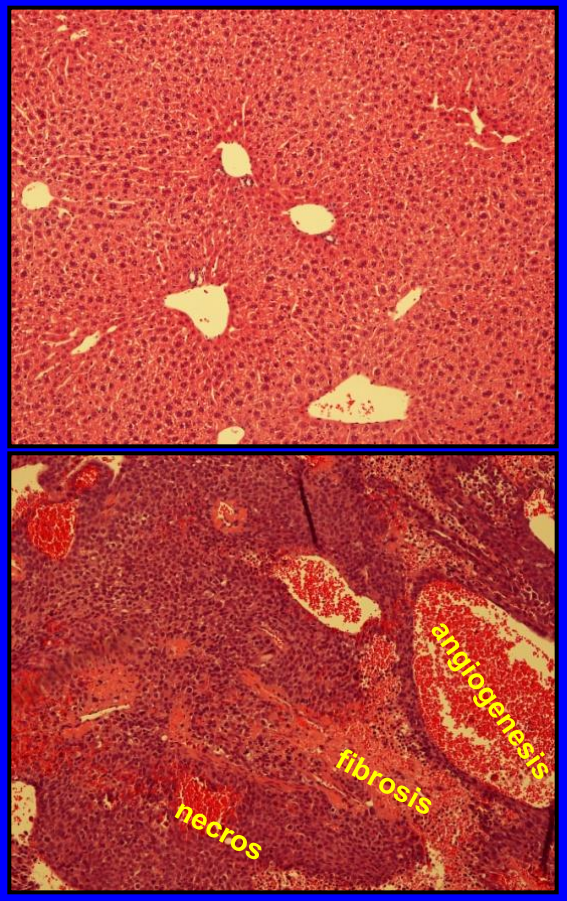
Intra-hepatic injection and subsequent passage



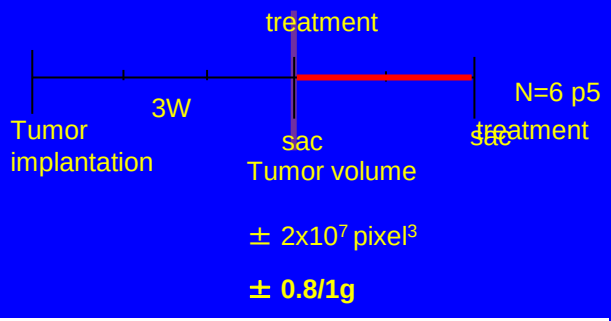


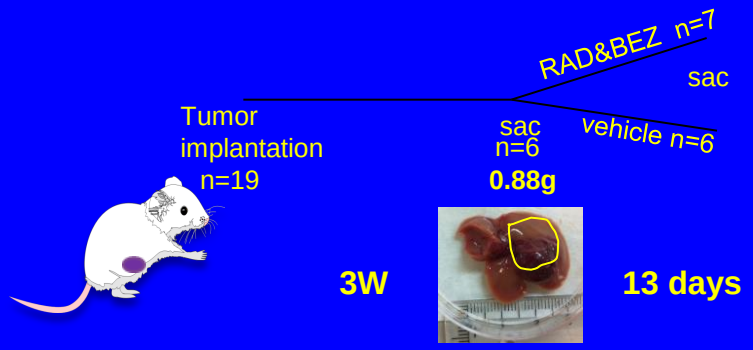
Healthy liver

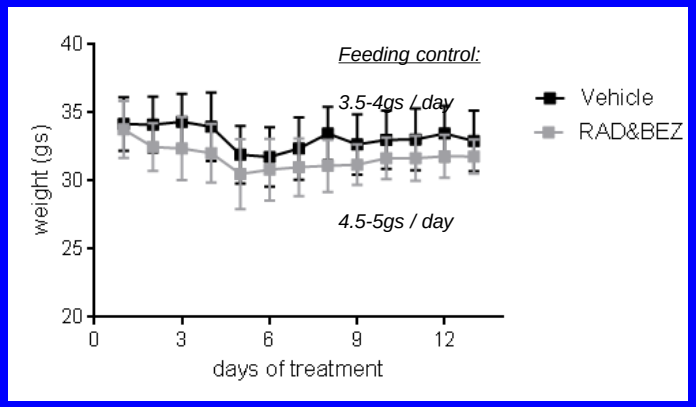
HCC

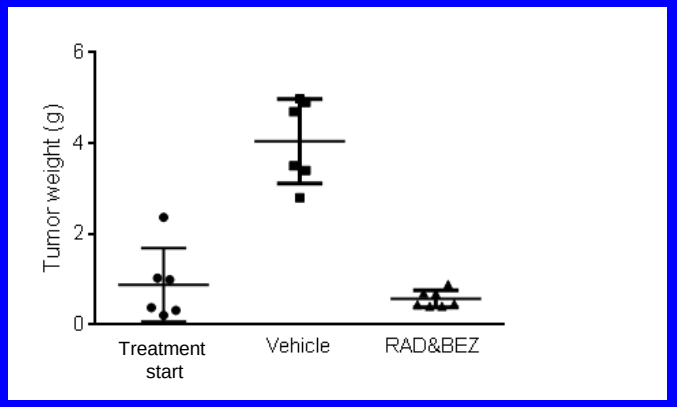


RAD/BEZ Treatment of established Huh7 tumors:

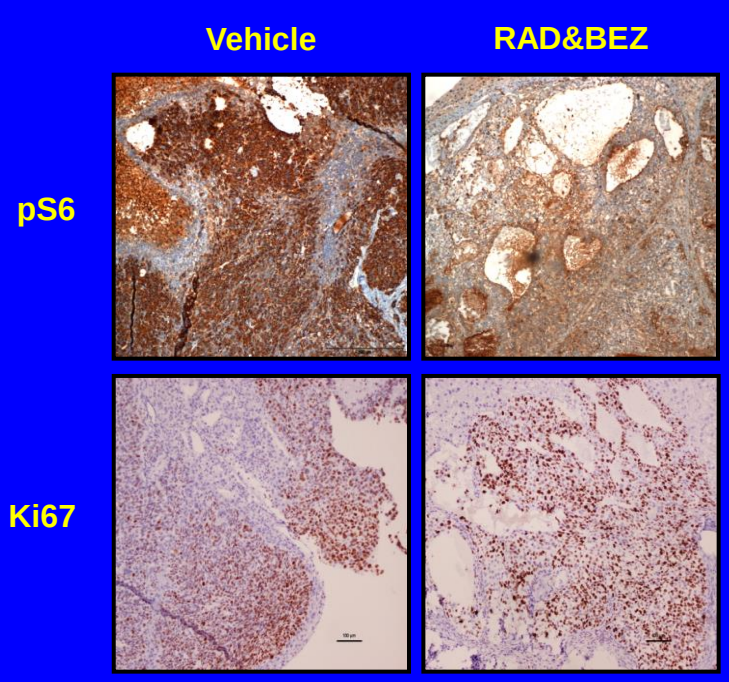


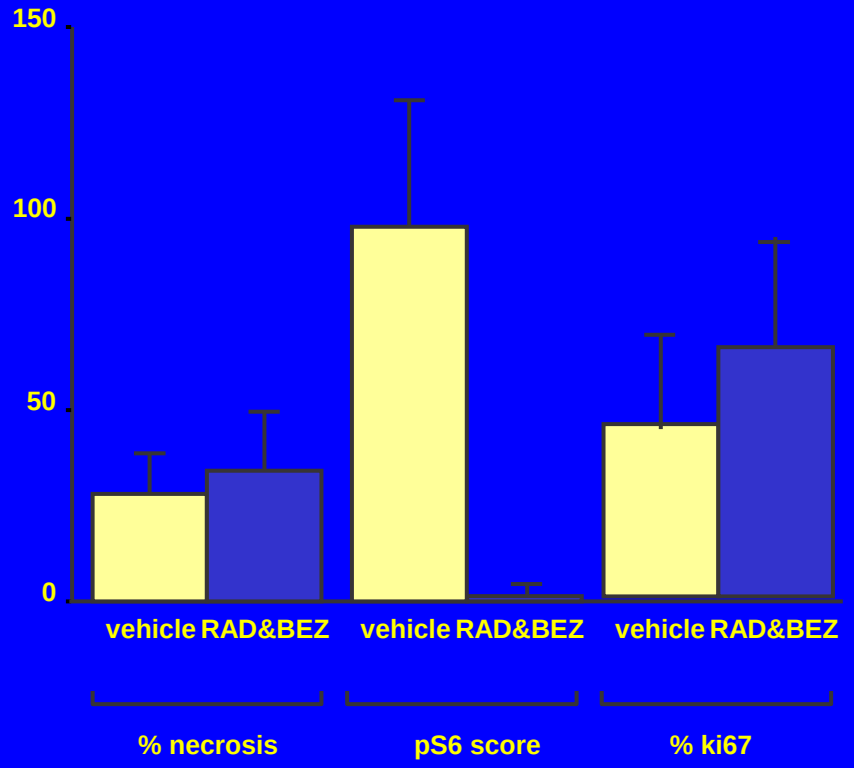




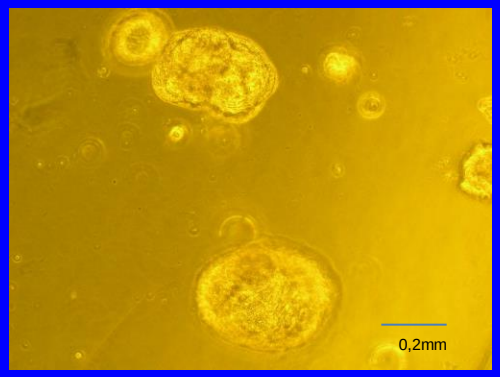


BEZ/RAD Treatment of Huh7 Tumors

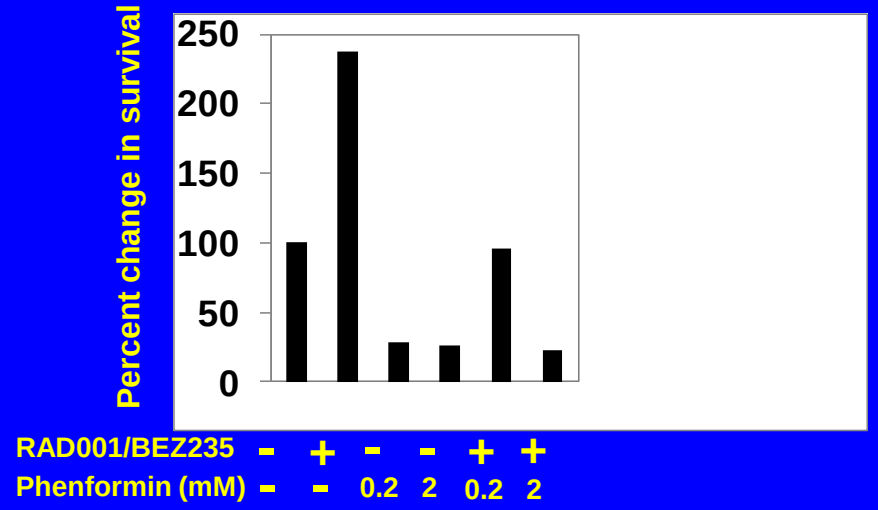




Organoids from HCC and triple combination



Organoids



Collaborators:

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Neus Agell & Sonia Brun, Barcelona: **IDIBAPS**
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Group members of the Kozma/Thomas/Tauler Laboratory:

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Mouse and *HCC*:

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Ribosome Biogenesis:

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T. Teng, F. Riaño, S. Menoyo & G. Donati

Nutrient Signaling:

Mercer & F. Riaño

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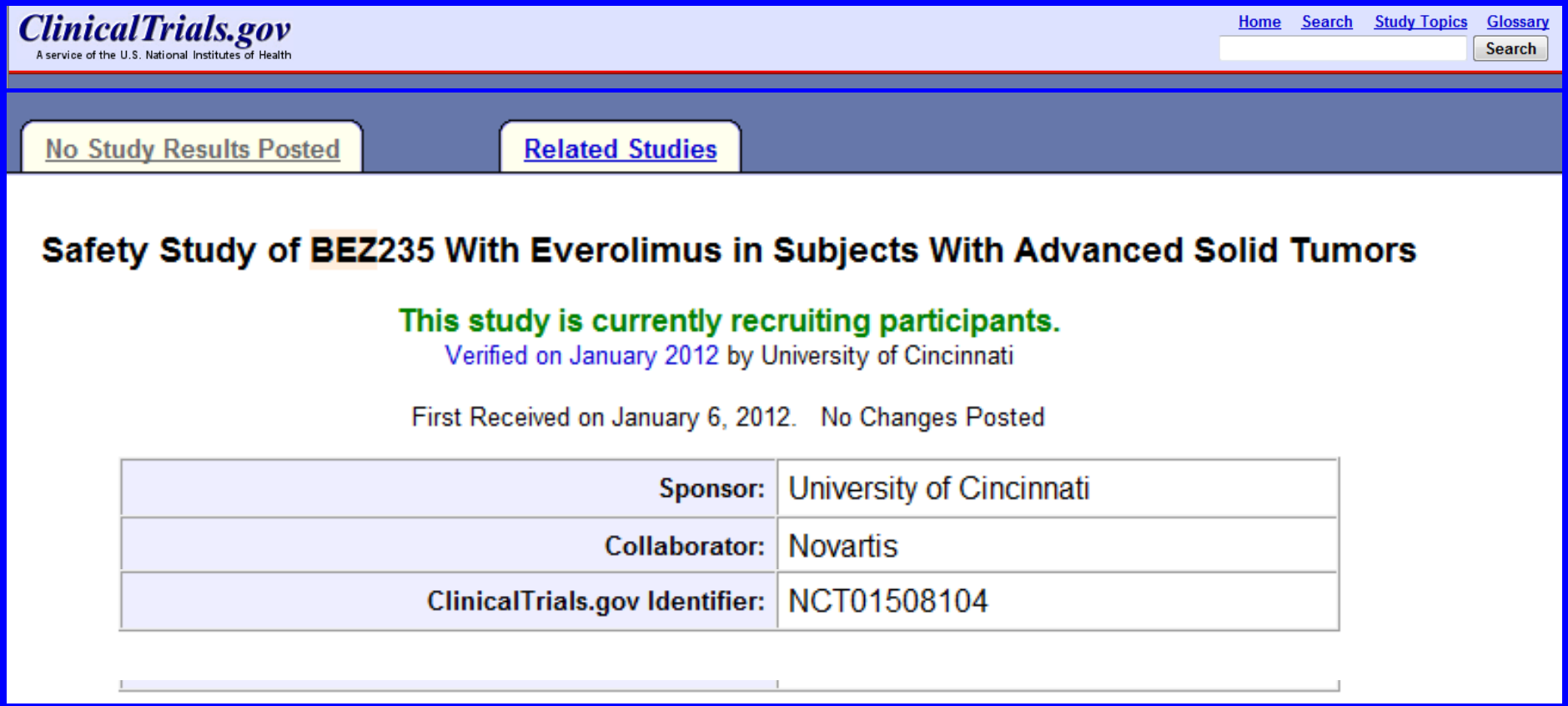
Translational Implication

Began an Investigator Initiated Phase 1B-2 dose escalation trial with RAD001 combined with BEZ235 in patients with advanced solid tumors, including HCC (funded by Novartis)



ClinicalTrials.gov
A service of the U.S. National Institutes of Health

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Safety Study of BEZ235 With Everolimus in Subjects With Advanced Solid Tumors

This study is currently recruiting participants.
Verified on January 2012 by University of Cincinnati

First Received on January 6, 2012. No Changes Posted

Sponsor:	University of Cincinnati
Collaborator:	Novartis
ClinicalTrials.gov Identifier:	NCT01508104